REMARKS/ARGUMENTS

The Office Action mailed November 5, 2003 has been carefully reviewed. Reconsideration of this application, as amended and in view of the following remarks, is respectfully requested. The claims presented for examination are: claims 1-19.

Objection to Drawings

The drawings were objected to as failing to comply with 37 CFR 1.84(p)(5) in the Office Action mailed November 5, 2003. The drawings are being replaced with a new set of drawings to add reference numeral 22 as required in the Office Action mailed November 5, 2003. A separate letter to the Office Draftsman is being submitted with a new set of drawings.

35 USC 103 Rejection

In numbered paragraph 6 of the Office Action mailed November 5, 2003 claims 1-19 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over the Krulevitch et al. references (U. S. Patent No. 5,985,217 and U. S. Patent No. 6,319,474) in view of the Wilding et al. reference (U. S. Patent No. 6,184,029).

Applicants' Claimed Invention - The claimed invention is described in Applicants' Application in some detail in the following paragraphs:

> Applicants' Application Paragraph [0010] "... an instrument having microfluidic channels connected at one end to a minimally invasive biopsy tool and at an opposite end with a PCR reaction chamber than can be integral with the microfluidic channels, or constructed to abut the channels for receiving sample therefrom."

> Applicants' Application Paragraph [0018] "The present invention involves an instrument for tissue biopsy and genetic analysis. The present invention provides the ability to take small tissue or blood samples in a minimally invasive manner from localized regions, then immediately perform DNA analysis through a real-time PCR with a portable

instrument. The present invention links the minimally invasive microbiopsy tool with specimen treatment microfluidic channels and a PCR reaction chamber into a single disposable device...."

Applicants' Application Paragraph [0026] "The embodiment of Figure 5 differs from that of Figure 4 in that the PCR chamber section is not integral with the microchannel and cutter sections, but is designed to mate directly with the microchannel section, as shown."

Applicants' Application Paragraph [0027] "It has been shown that the present invention provides a portable instrument that has the ability to take small tissue or blood samples in a minimally invasive manner from localized regions, then immediately perform the DNA analysis through real-time PCR. The PCR chamber can be integral with the biopsy and microchannel sections of the instrument, or be on a separate substrate with the capability to mate with the microchannel and biopsy substrate."

Applicants' Application Paragraph [0028] "This instrument enables genetic analysis in the field by providing a hand held device, and the instrument can be used to rapidly detect and identify people or the presence of disease, with applications in both military and civilian sectors. The instrument provides the capability for biopsy and genetic analysis of tissue and blood cells, for the study of existing or potential medical disorders."

The Wilding et al. Reference - The Wilding et al. reference (U. S. Patent No. 6,184,029) shows only two PCR chambers in the many different versions of the devices disclosed in the patent. As described in the Wilding et al. reference,

"FIG. 11A diagrammatically depicts an analytical device 191.... a polynucleotide amplification chamber comprising sections 198a and 198b," and "Another embodiment of an analytical device which is useful in the practice of this invention is illustrated in FIG. 11B. The device 210 comprises a substrate 214 microfabricated with a mesoscale polynucleotide amplification chamber 222A."

As described in the Wilding et al. reference, "The sample preparation device of the invention comprises a solid substrate, preferably in the form of a chip having dimensions on the order of less

than one to a few millimeters thick and approximately 0.1 to 5.0 centimeters square. The substrate is microfabricated to form a sample flow path having an inlet and an outlet as well as a separator disposed intermediate to the inlet and outlet. The upstream-facing portion of the separator defines a separation zone in the flow path in which particulate components of the test sample are collected. The device may also include a flow channel in fluid communication with the separation zone which functions to discharge collected particulate components from the separation zone. The flow channel has an inlet section for directing a carrier fluid into the separation zone and over the upstream-facing portion of the separator and a discharge section for directing the carrier fluid, in which the particulate components are entrained, out of the separation zone. At least one of the aforementioned flow path and flow channel sections has at least one mesoscale dimension."

"Initially, the valves in the above-mentioned appliance function to close ports 193c and 193d, while ports 193a and 193b are open. A sample containing a mixture of cells, e.g., transferred from the sample preparation device, is directed to the sample inlet port 193a by a suitable impellent, e.g., a pump, (not shown), and flows through the mesoscale flow channel 194a to separation chamber 196a. Chamber 196a contains binding moieties immobilized on the wall of the chamber which selectively bind to a surface molecule on a desired cell type in the sample. Remaining cellular components exit the substrate via port 193b. After binding of the desired cell type in chamber 196a, flow with buffer is continued, to wash and assure isolation of the target cells. Next port 193b is closed and 193c is opened. Flow is then increased sufficiently to dislodge the immobilized cells from chamber 196a. Flow is continued, forcing cells through membrane piercing protrusions 195 in chamber 196b, which tear open the cells releasing intracellular material."

"Sample flow continues past filter 197, which filters off large cellular membrane components and other debris, with the filtrate passing to mesoscale PCR chamber section 198a, which is connected to PCR chamber section 198b by flow channel 194b. Tag polymerase, primers and other reagents required for the PCR assay next are added to section 198b through port 193c from a source thereof (not shown), permitting mixing of the intracellular soluble components from the

separated subpopulation of cells and the PCR reagents. With the ports closed (to ensure that the reaction mixture does not evaporate, or otherwise becomes lost from the device), an impellent, e.g., a pump, (not shown), applies a motive force to port 193b to cycle the PCR sample and reagents through flow channel 194b between sections 198a and 198b, set at 94.degree. C. and 65.degree. C., respectively, to implement plural polynucleotide melting and polymerization cycles, allowing the amplification of the polynucleotide of interest. Before the next process step, port 193c is closed and port 193d is opened. The same impellent force is then used to direct the amplified polynucleotide isolated from the cell population to a detection region 199 in the form of a pattern of flow channels like that described above with reference to FIG. 9C. Flow reduction in the restricted region serves as a positive indicator of the presence of amplified polynucleotide product and may be detected optically through a glass cover disposed over the detection region 199. Alternatively, the amplified polynucleotide product may be detected directly in the reaction chamber, using commercially available reagents developed for such purpose, such as the "Taq Man.RTM." reagents, available from Perkin Elmer Corporation. The amplified polynucleotide may also be detected outside the device using various methods known in the art, such as electrophoresis in agarose gel in the presence of ethidium bromide."

"In operation, a sample containing polymerase enzyme and other reagents required for PCR is delivered through inlet port 216A to reaction chamber 222A. With the ports closed, a heating element is then utilized to thermally cycle the reaction chamber between a temperature suitable for dehybridization and temperatures suitable for annealing and polymerization. When the PCR reaction cycle is terminated, ports 216B and 216D are opened, driving the contents of chamber 222A to detection region 222B, which region contains a polynucleotide probe, e.g., immobilized upon beads 292. A positive assay for the polynucleotide is indicated by agglutination of the beads in the detection region."

Applicants Response to the 35 USC 103 Rejection

Applicants respectfully submit that the invention defined by the claims now presented for examination is patentable over the three references cited in the

Office Action mailed November 5, 2003. The three references are: Krulevitch et al. (U. S. Patent No. 5,985,217), Krulevitch et al. and U. S. Patent No. 6,319,474), and Wilding et al. (U. S. Patent No. 6,184,029). All of the independent claims now in the application have been amended and now include a combination of elements not shown by the references or any legitimate combination of the three references. For example, amended claim 1 now includes the following combination of elements: "a cutter section, a specimen chamber located below said cutter section, a specimen treatment section located adjacent said specimen chamber, and a PCR reaction chamber section that is integral with said specimen treatment section or abuts said specimen treatment section."

None of the three references show Applicant's claimed combination. The only reference that even mentions a "PCR reaction chamber" is the Wilding et al. reference which shows only two PCR chambers in the many different versions of the devices disclosed in the Wilding et al. reference. The Wilding et al. reference "polynucleotide amplification chamber 198a and 198b" and "polynucleotide amplification chamber 222A" only appear in figures 11A and 11B of the Wilding et al. reference. Chamber 198a and 198b and chamber 222A are part of a complex arrangement of structure. It would not be obvious to combine the chamber 198a and 198b and chamber 222A of the Wilding et al. reference with either of the Krulevitch et al. references and any such combination would still not show the invention defined by Applicant's amended claims.

The MPEP section 706.02(j) "Contents of a 35 U.S.C. 103 Rejection," states: "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The

teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

Applicants respectfully submit that there can be no combination of the three references Krulevitch et al. (U. S. Patent No. 5,985,217), Krulevitch et al. and U. S. Patent No. 6,319,474), and Wilding et al. (U. S. Patent No. 6,184,029) that would meet the three criteria set out in MPEP section 706.02(j) "Contents of a 35 U.S.C. 103 Rejection."

First, there is no suggestion or motivation to modify the reference or to combine reference teachings of the three references to produce the invention defined by Applicant's amended claims. None of the three references show or suggest Applicant's claim elements. Since none of the three reference show Applicant's claim elements, there can be no combination of the references that show Applicant's claim elements.

Second, there would not be a reasonable expectation of success of any combination of the three references. There is no teaching of how the structure in the Wilding et al. reference would be combined with the structure in the Krulevitch et al. references.

Third, only through impermissible hindsight would any motivation be found to combine the structure in the Wilding et al. reference with the structure in the Krulevitch et al. references. MPEP §2142 states "the tendency to resort to 'hindsight' based upon applicant's disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art." Also, under MPEP §2143.01, "the mere fact that references can be combined or modified does not render the resultant

combination obvious unless the prior art also suggests the desirability of the combination." In re Mills, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

Applicants believe they have provided a full and complete response to the 35 U.S.C. 103 Rejection in numbered paragraph 6 of the Office Action mailed November 5, 2003.

Obviousness-Type Double Patenting Rejection

In numbered paragraph 7 of the Office Action mailed November 5, 2003 claims 1-19 were rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1-15 of the Krulevitch et al. reference (U. S. Patent No. 5,985,217) in view of the Wilding et al. reference (U. S. Patent No. 6,184,029).

Applicants Response to the Obviousness-Type Double Patenting Rejection

As explained above in connection with Applicants response to the 35 USC 103 rejection, all of the independent claims now in the application have been amended and now include a combination of elements not shown by the references or any legitimate combination of the three references. The above arguments are incorporated herein rather than repeating the arguments. Applicant's invention, as defined by the claims now presented for examination, are believed to be patentable.

Applicants believe they have provided a full and complete response to the obviousness-type double patenting rejection in numbered paragraph 7 of the Office Action mailed November 5, 2003.

SUMMARY

The undersigned respectfully submits that, in view of the foregoing amendments and the foregoing remarks, the rejections of the claims raised in the Office Action dated November 5, 2003 have been fully addressed and overcome, and the present application is believed to be in condition for allowance. It is respectfully requested that this application be reconsidered, that the claims be allowed, and that this case be passed to issue. If it is believed that a telephone conversation would expedite the prosecution of the present application, or clarify matters with regard to its allowance, the Examiner is invited to call the undersigned attorney at (925) 424-6897.

Respectfully submitted,

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Livermore, California
Dated: January 30, 2004